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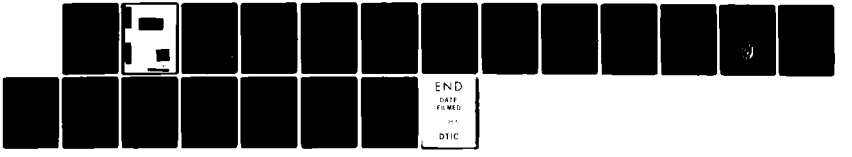

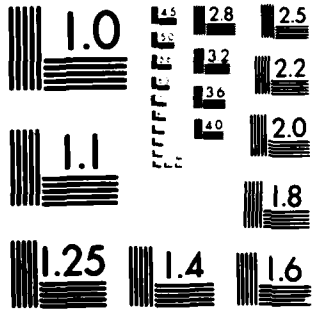

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THE MAXIMAL EXERCISE TREADMILL STRESS TEST
Current Uses and Limitations in Coronary Artery Disease

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DEPARTMENT OF NATIONAL DEFENCE - CANADA

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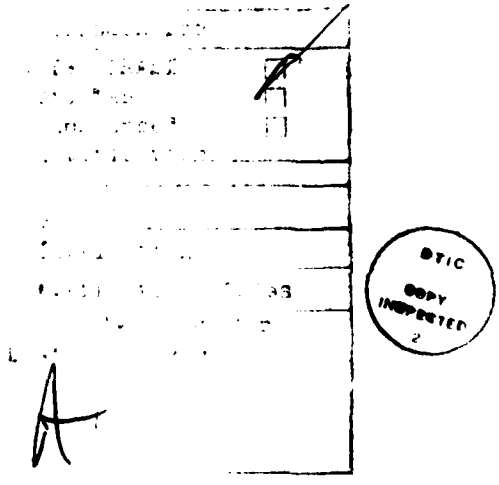

ABSTRACT

Considerable controversy surrounds the clinical value of exercise stress testing, particularly in the diagnosis of coronary artery disease (CAD). For example, ECG ST segment depression during exercise (the classic criterion for a "positive" test) may have only limited diagnostic worth in a population with low disease prevalence. Conversely, a "negative" test result may have questionable value in a population with high disease prevalence. On the other hand, ST segment measurement represents only one important observation that can be made during the test procedure: increased predictive accuracy for CAD may result if additional clinical patient responses (e.g., blood pressure) are considered along with ECG interpretation.

A review of recent literature indicates that a critical evaluation of the clinical importance of exercise stress testing continues. This paper presents current applications and limitations of exercise stress testing in CAD, and examines the predictive accuracy of this diagnostic approach.

INTRODUCTION

Coronary artery disease (CAD) continues to plague Western societies, causing significant rates of morbidity and mortality, often striking people during their most productive years. Unfortunately, some 65% of fatalities occur unexpectedly, without prior symptoms (1). Approximately 10% of all males aged 40-60 years will experience some symptom or sign of severe CAD: classic angina, myocardial infarction or sudden death.

Military populations, who might be thought to be somewhat fitter than normal populations, are similarly prone to develop and suffer the complications of CAD. DeHart (2) reports that 10-20% of USAF pilots could be expected to have a significant degree of coronary atherosclerosis, making future aviation accidents due to aircrew incapacitation a very real possibility. He further estimates that the USAF suffers a $50 million annual loss because of costs associated with CAD-induced non-effectiveness, personnel replacement, medical care, and disability and death benefits.

Clinical tests devised to diagnose the presence and severity of CAD, before its potentially fatal manifestations emerge, are important not only in providing appropriate medical care to a given patient, but also in predicting the future operational effectiveness of any military/civilian population especially where members' ages exceed 35 years.

Many forms of exercise testing have long been utilized in the appraisal of cardiopulmonary or general physical fitness. In 1908, Einthoven (3) published post-exercise ECG tracings, although he did not comment on the significance of observed ST segment changes. Twenty years later, Feil and Segal (4) exercised patients with CAD, and reported ECG repolarization changes coincident with the development of anginal pain. The Harvard Step Test (5) was developed in 1942 to measure fitness in athletes and military subjects: heart rate was monitored during recovery from exercise to provide an index of aerobic power. The modern approach to stress testing dates from 1956 when Bruce (6) described a treadmill work test and guidelines to allow grouping of patients into heart disease classifications. More recent developments have included the computerized assessment of post-exercise ECG patterns, and the arteriographic and scintigraphic correlations between exercise-predicted and actual levels of CAD. The exercise stress test has actually slowly evolved over some 75 years, to yield a clinical procedure still useful in the detection and evaluation of CAD.

Myocardial ischemia results when the coronary circulation is unable to maintain a supply of oxygen sufficient to meet increasing cardiac tissue demands. This imbalance typically occurs during

exercise, after a major coronary artery has developed atherosclerotic narrowings greater than 70%. Under resting conditions, however, coronary blood flow may remain adequate even with severe stenosis (up to 90% occlusion).

Properly applied exercise will stimulate all the major determinants of an increased myocardial oxygen requirement: increased heart rate, blood pressure, intramyocardial tension, and velocity of contraction of the myocardium. The exercise test thus provides an excellent resource for detecting susceptibility to cardiac dysfunction in association with increased physiologic workload, by stressing the heart's reserve capacity. Modern treadmill ergometers allow patients a controlled progression from mild to strenuous exercise, with predictable increases in myocardial oxygen demand. Table 1 outlines the progressing workload and oxygen requirements met during exposure to the currently popular Bruce Treadmill Exercise Protocol.

Table 1. The Bruce Protocol

Stage	Time (min)	Speed (mph)	Grade (%)	Oxygen Requirement (ml/kg/min)	Workload (mets)
I	3	1.7	10	17.5	5
II	6	2.5	12	24.5	7
III	9	3.4	14	33.3	10
IV	12	4.2	16	45.5	13
V	15	5.0	18	63.0	18

Even patients with significant levels of CAD may be adequately protected from rapid increases in myocardial demand. Indeed, the popularity of exercise stress testing has resulted not only from its low cost and non-invasive nature, but also from its very low risk. Bruce (7) has reported no deaths and only 6 instances of cardiac arrest in nearly 26,000 tests performed in the Seattle area over the last nine years.

This report deals specifically with the application of a controlled physical stress in the diagnosis and assessment of CAD, through examination of the ECG and the clinical response of the patient.

TEST INTERPRETATION

The classic criterion for exercise-induced myocardial ischemia has been electrocardiographic ST segment deviation. Normally, increases in heart rate associated with exercise may cause a progressive depression of the junctional "J-point", with a rapid return of the ST segment to the isoelectric baseline. Froelicher (8) has reported that these physiologic exercise-induced junctional

depressions are the result of competition between normal repolarization and delayed terminal depolarization forces. Kattus (9), however, suggested that this ECG change might be just a first stage in the development of a significant ischemic response, where follow-up stress tests would eventually reveal more classical deviation. (He was able to abolish simple J-point depression in some exercising patients with sub-lingual nitroglycerin.)

A classic positive "ischemic" response has usually been described as a greater than 1.0 mm ST segment depression which persists for 0.08 seconds before returning to baseline. Now, considerable discussion has also developed regarding the shape or contour of the ST segment (see Fig. 1). Horizontal "square wave" or downsloping depressions are invariably thought to represent "positive" tests, but the importance of upsloping ST depression is less clear. Stuart and Ellestad (10) reported that slowly upsloping ST depression (2 mm persisting past 0.08 seconds) carried the same prognostic significance as horizontal ST segment depression. Chaitman (11) recommended inclusion of slowly-upsloping ST depression greater than 1.0 mm as a "positive" test criterion, noting that with 14-lead ECG monitoring, at least one lead would record horizontal or downsloping changes if upsloping changes were observed in other leads.

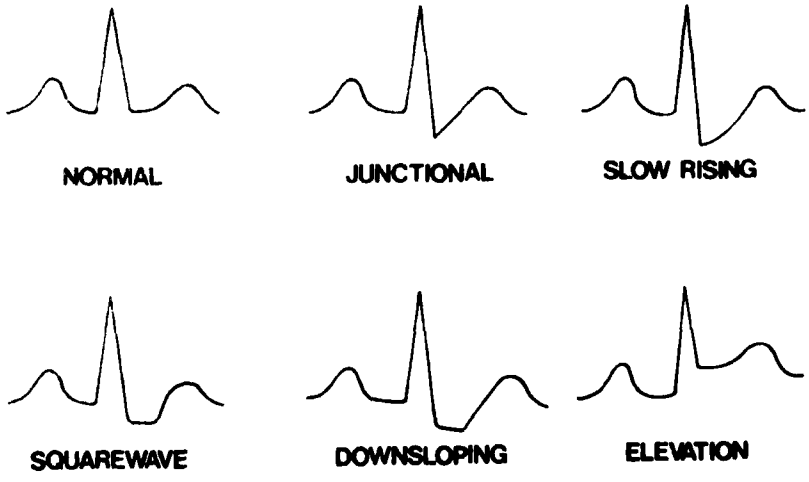

Figure 1. Patterns of ST segment behaviour induced by exercise. (From Fortuin and Weiss, CIRCULATION Vol. 56, No. 5, Nov. 1977).

Goldschlager's study (12), however, indicated that upsloping ST depressions should best be considered as "equivocal" responses, to be interpreted in the light of other clinical data; further studies are required to properly elucidate their significance.

ST segment elevation, seen only rarely with exercise, may indicate severe myocardial ischemia of transmural extent, or may reflect abnormal left ventricular wall motions. Recently, Specchia (13) published data to show that exercise-induced ST segment elevation in patients without a history of myocardial infarction or left ventricular aneurysm may be caused by coronary spasm of a major coronary vessel (Prinzmetal's phenomenon).

Further debate exists over the interpretation of other exercise-induced ECG changes, as reviewed by Sotobata (14). Flattening or inversion of positive T-waves is thought to be a physiologic response to exercise, while normalization of inverted T waves may occur in patients with or without CAD. The rare phenomenon of positive U wave inversion may indicate the presence of CAD, particularly when the resting ECG is normal. Decreases in R wave amplitude may be seen in normal exercising subjects; increases or no change in this measurement has been postulated as evidence of myocardial ischemia, particularly where seen in conjunction with ST segment depression. The diagnostic worth of all of these assessments is still controversial.

Of course, ST segment changes labelled as "ischemic" only provide evidence of coronary perfusion deficits. Patients should also be screened to rule out other potential cardiac dysfunction (e.g. aortic valve disease) which may also compromise coronary blood flow in the presence of normal coronary arteries. It's also well known that a variety of other disorders or physiologic states will give rise to electrocardiographic test results which mimic myocardial ischemia (see Table 2).

Table 2. Clinical States Capable of Producing False Positive Exercise Tests.

1. Medications: Digitalis, diuretics (potassium depletion), sedatives, anti-depressants
2. Valvular heart disease, including mitral valve prolapse.
3. Left or right ventricular hypertrophy (congestive myocardiopathy): presumed hemodynamic deprivation of subendocardial perfusion.
4. WPW syndrome or LBBB (repolarization abnormalities)
5. Vasoregulatory Asthenia (overactive sympathetic nervous system)
6. Non-fasting state
7. Hyperventilation (electrolyte shifts)
8. Hypertension

In addition to ECG changes, other objective and subjective

responses to exercise have to be reviewed critically in assessing whether a given test has produced a "positive" or "negative" result. Wenger (15) notes, for example, that a patient who exhibits a significant drop in blood pressure with modest exercise may be manifesting "inotropic incompetence", suggestive of severe left ventricular ischemic dysfunction. Patients with evidence of other clinical abnormalities in the course of testing (i.e., unusual dyspnea, ataxia, lightheadedness) may well be suffering inadequate cardiac output, possibly due to myocardial ischemia.

Several authors (16-18) have called for a more rational approach to exercise test interpretation, where the ECG ST segment response to exercise is viewed as only one feature to be examined in the prediction of cardiac dysfunction. Table 3 lists other clinical variables to be critically considered in assessing a given patient's response to exercise. Further work to establish appropriate weighting values for each variable in a multi-factorial prediction of CAD may further enhance the clinical value of exercise testing.

Table 3. Clinical Exercise Predictors of CAD (other than ST segment changes)

1. Failure to achieve 90% of the maximal age-predicted heart rate.
2. Inability to increase systolic blood pressure (e.g. by 10 mmHg over 2 stages of the Bruce protocol).
3. Increase in diastolic blood pressure greater than 15 mmHg.
4. Chest pain during maximal exertion.
5. Short duration of exercise.
6. Development of cardiac dysrhythmia.
7. Appearance of 3rd or 4th heart sounds post-exercise.

Ellestad (19) examined 96 patients with normal coronary angiograms, who scored a "positive" exercise test on the basis of ST depression alone. By comparing them to 128 other patients with "true positive" tests, and by assessing an additional eleven patient variables in a computerized multi-variate analysis, he reported the ability to re-classify 65% of the "false positive" tests as "true negatives". He emphasized, however, that the term "false positive" may be a misnomer, because the absence of coronary artery disease does not necessarily mean that the myocardium, the source of the abnormal repolarization, is also normal. He speculated that ST depression may always indicate some metabolic abnormality in cardiac functioning, despite the presence of angiographically-normal coronary arteries.

PREDICTIVE POWER: THE MAJOR LIMITATION

The major limitation of the exercise stress test is based on the fact that it is simply not a "perfect" diagnostic assessment. Some patients with coronary artery disease will demonstrate a "normal" test

(false negative result), while others without significant disease will register an "abnormal" test (false positive result). Obviously, predictive accuracy will be defined by statements of test sensitivity and specificity (see definitions below), but, in addition, limits of statistical reliability will be influenced by the prevalence of the disease in the population being studied. This results partly from the fact that when test specificity is less than 100%, some proportion of normal patients must show a false positive result; the predictive value of a positive test is hence diminished according to the percentage of normal subjects in the population being tested.

Bayes' Theorem of conditional probability, first presented in 1763 (20), has been adapted to demonstrate the manner in which the predictive power of a clinical test can be limited by disease prevalence. A test's "predictive value", or, its ability to measure the probability that a person with a positive test has the disease being tested for, is described as follows:

$$\text{Predictive Value} = \frac{\#\text{ true positives}}{\#\text{ true positives} + \#\text{ false positives}}$$

$$= \frac{(\text{Sensitivity} \times \text{Prevalence})}{(\text{Sensitivity} \times \text{Prevalence}) + [(1 - \text{Prevalence}) \times (1 - \text{Specificity})]}$$

Where:

True positive = Abnormal test result in a patient who has the disease being tested for.
False positive = Abnormal test result in a patient who does not have the disease.
True negative = Normal test result in a patient who does not have the disease
False negative = Normal test result in a patient who has the disease.

$$\text{Sensitivity} = \frac{\text{number of true positive tests}}{\text{total number of patients with disease}}$$

$$\text{Specificity} = \frac{\text{number of true negative tests}}{\text{total number of patients without disease}}$$

$$\text{Prevalence} = \frac{\text{number of patients with disease in test population}}{\text{total number of patients in test population}}$$

$$\text{Rarity} = (1 - \text{Prevalence}) = \frac{\text{number of patients without disease in test population}}{\text{total number of patients in test population}}$$

Once clinical experience has determined the sensitivity and specificity of a test, then predictive values for test results can be calculated for given clinical patient subsets (with varying disease

prevalence). Hollenberg (21) published results from 10 separate studies (1967-1976) comparing exercise testing predictions against coronary arteriography; mean sensitivity was reported as 68%, specificity as 92%. Using these mean values, therefore, a "positive" test in a young asymptomatic male (CAD prevalence approximately 3%) yields a predictive value of only 16% (i.e., only 16% of the positive tests will reflect true disease). On the other hand, in a symptomatic middle-aged male (where disease prevalence has increased to 50%) a positive test increases predictive value to 86%.

Forrester and Diamond (22) have graphically presented the importance of this statistical approach in assessing the clinical value of a positive exercise test (see Fig. 2). The probability that a positive exercise test will predict CAD can be seen to range from 1% to 99%, depending on the initial clinical presentation of the patient. Assuming, automatically, that a positive test is evidence of myocardial ischemia could be highly misleading, and unfairly traumatic to the patient under review. A probabilistic approach to CAD diagnosis, based on Bayes' Theorem, could help physicians better understand the implications of test results, as well as reduce the risk of creating iatrogenic cardiac "cripples". It should be cautioned, of course, that such statistical analyses should only support, not replace, sound clinical judgement.

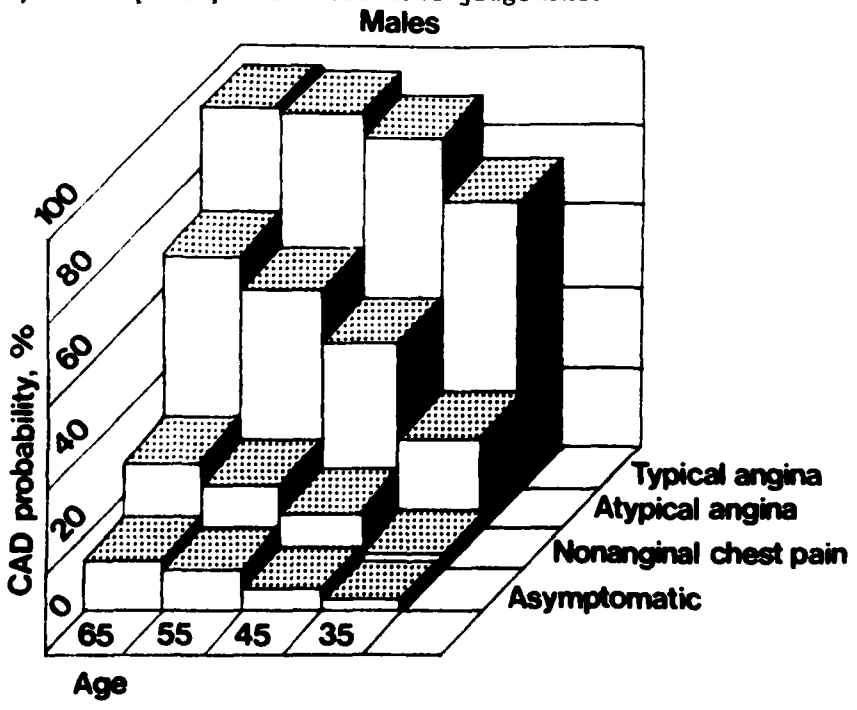

Figure 2. The significance of a "positive" ECG stress test in males. Patient group is subdivided by probability of CAD (y axis), by age (x axis), and by symptoms (z axis).

CURRENT APPLICATIONS IN CAD

Recent data allowing comparison of coronary arteriography to predictions from exercise stress testing has shown a disturbingly high number of false positive and false negative measurements. If, however, it's recalled that the exercise test is designed to complement sound overall clinical judgement, then uncertain applications in particular populations should not lead to an outright rejection of the method. Certainly it still serves as a valuable diagnostic aid in assessing patients with known or suspected CAD; in certain asymptomatic groups, it may still prove useful, provided that results are examined cautiously. In this regard, the Council on Scientific Affairs of the JAMA (23) recently published guidelines to describe current applications for exercise stress testing:

1. Diagnosis of Chest Pain: Perhaps the most common usage is in the evaluation of chest discomfort, particularly when clinical findings are suggestive, but not diagnostic of CAD. In this setting the exercise test will help establish a probability of significant disease. McGuire (16) has noted that the increased prevalence of disease in this population leads to a higher predictive accuracy for the exercise test. If 70% luminal coronary obstructions on arteriography are taken as reference standards, then 65-85% of symptomatic patients will show an abnormal exercise test. In patients with "atypical" chest pain, but no other signs of heart disease, the practice of using a negative treadmill test as a basis for patient reassurance and conservative management seems appropriate.

2. Patient Prognosis: In patients with known CAD, the exercise test may serve as an excellent prognostic device (risk of later morbidity or mortality). Braunwald (24) reviews data which suggests that patients who display ischemic responses at mild exercise levels have a greater than 50% chance of developing significant CAD within four years, while those who show such changes only with strenuous exercise have a less than 20% likelihood of disease progression (see Figure 3). These prognostic effects prevailed also in survivors of myocardial infarction: four years after testing, patients with abnormal treadmill responses had 30% greater progression of CAD than did survivors with a normal test response.

Both Bruce (6) and McNeer (25) have suggested routine office exercise testing as a continual follow-up for CAD patients in selecting an optimal time for further invasive study and aorto-coronary bypass surgery. Bruce's experience has allowed management of anginal patients for up to three years before evidence of left ventricular dysfunction (cardiomegaly, failure to reach Stage II of the Bruce protocol, and/or peak exercise systolic blood pressure less than 130mm Hg) has emerged, thereby indicating the need for invasive intervention.

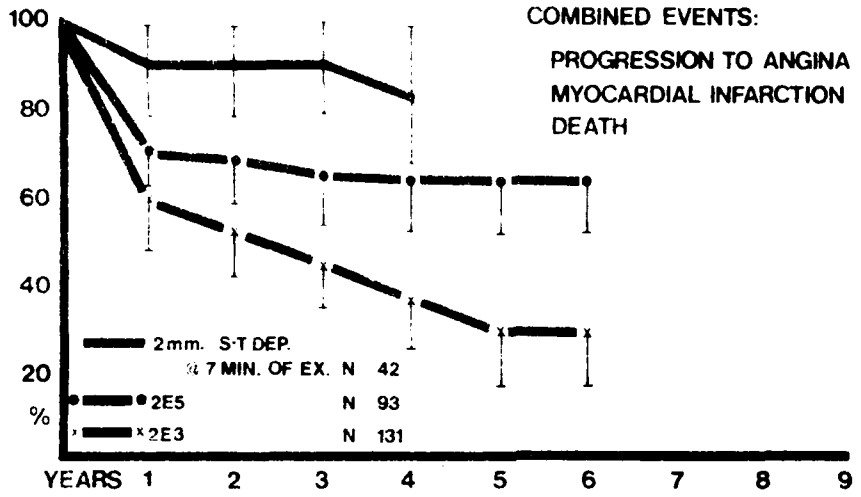

Figure 3. Graph plots % chance of survival without progression to angina or myocardial infarction against years of survival for patients who exhibited ST depression after 7, 5, or 3 minutes of exercise. Healthy survival is proportional to exercise capacity. (from: Ellestad, M.H.: Stress Testing: Principles and Practice, Philadelphia, F.A. Davis Co., p. 167, 1975.)

3. Evaluation of Functional Capacity: The best non-invasive estimation of cardiac functional capacity is the direct measurement of maximal oxygen consumption, VO_2max (i.e., the amount of oxygen consumed per unit body weight per unit time) while a patient is exercising at maximal workload. Although large biologic variations may exist in given populations, and although VO_2max has not been as carefully evaluated as exercise-induced ECG changes, measurement of oxygen consumption may help indicate significant hemodynamic impairment. Froelicher et al. (26) showed severe cardiac impairment with maximal oxygen consumption values less than 16 ml per kgm per min, and increased potential for development of cardiac symptoms at values less than 22 ml/kgm/min. In addition, establishment of

endurance, allows a rational determination of appropriate activity level for occupation or recreation in all types of cardiac disease (through correlation of energy costs of required tasks to formally-measured exercise capacity).

4. Dysrhythmia Evaluation: A principal risk of exercise is the development of associated dysrhythmia, especially for patients with coronary artery disease. Such a risk becomes an important public health issue where patients are involved in hazardous activities or occupations where coordination and alert performance affects the lives or safety of others. In patients with no other evidence of CAD, frequent ventricular extra-systoles that disappear with exercise probably do not constitute a major risk. In insurance groups, supra-ventricular dysrhythmias brought on by exercise do not seem to have any effect on long-term mortality rate figures (27). When, however, ventricular dysrhythmia is induced by exercise, underlying myocardial ischemia may be suspect (28). Ventricular dysrhythmia recorded in a patient with known CAD increases his risk of a serious coronary event by two to three times, and complex ventricular dysrhythmias after myocardial infarction increase the likelihood of sudden death to 30% in 30 months (29).

5. Treatment Evaluation/Exercise Prescription: The value of various treatment modalities for CAD (e.g., rehabilitation training programs, medications such as beta-blockers, or aorto-coronary bypass surgery) can be critically assessed via exercise testing. Increases in maximal oxygen uptake or reductions in blood pressure or heart rate responses at a given workload would suggest positive results from therapy. Safe guidelines for exercise prescriptions, particularly following myocardial infarction, are best derived from direct measurements of maximal oxygen uptake and heart rate during exercise testing. Patients' progress can also be monitored effectively through the serial assessment of improvements in exercise endurance to stages where chest pain or ECG changes develop.

6. Screening for CAD: By far the most controversial application of exercise stress testing is in reviewing asymptomatic populations, as a screen for latent CAD. Kunkes (30) points out that myocardial ischemia occurs without pain, and that painless ST segment deviation occurring during exercise testing, may indicate the presence of disease. However, the low prevalence of CAD in asymptomatic groups would lead to an unacceptably high number of false positive tests. On the other hand, Amsterdam (31) offers a hypothetical example to illustrate that the risk for CAD is still considerably higher in "normals" who show a "positive" test than in those with a "negative" test (see Table 4).

Table 4. The Relation of Exercise ECG Results to Prevalence of Coronary Artery Disease and to Sensitivity and Specificity of the Test (Assume Disease Prevalence 5%, Sensitivity 60%, Specificity 90%).

No. Subjects	Positive ECG Results	Negative ECG Results
Normal (95%): 950	95 (10% FP)	855 (90% TN)
CAD (5%): 50	30 (60% TP)	20 (40% FN)
1000	125	875

Then, for calculating risk for CAD:

A. With positive test: $= \frac{30}{125} = 24\%$

B. With negative test: $= \frac{20}{875} = 2.3\%$

$$\therefore \text{Risk ratio} = \frac{\text{Positive test}}{\text{Negative test}} = \frac{24}{2.3} = 10.4$$

Hence, asymptomatic people with a positive test have a 10-times higher risk for CAD than those with a negative test. Clinical follow-up tends to support this mathematical model. Froelicher (32) examined 1390 asymptomatic men for a mean follow-up of 6.3 years, and reported that a positive ECG stress test identifies a group of men with a risk for CAD 14.3-times higher than those with a negative test.

Herman (33) has adopted a fairly aggressive approach, to say that a coronary arteriography study is definitely indicated in any asymptomatic person with a positive stress test, particularly where ST segment depression is 2 mm or more. On the other hand, Hickman (34) has published data to indicate the lack of return gained from a program of routine unstructured exercise testing among asymptomatic individuals. A U.S. Air Force Command conducted 775 stress tests in men over the age of 37 years. Only 7.7% showed abnormal tests (60 patients) and of these, only four cases of significant CAD were determined (two of these were suspended from flying activities, and two were waivered for flying). Although Hickman points out that absence of symptoms does not rule out the presence of severe obstructive CAD, and that from an aeromedical standpoint, even mild degrees of CAD can lead to sudden incapacitation during positive Gz manoeuvres, he concludes that unstratified exercise testing gives an unacceptable yield of CAD, related to the logistical expense involved.

SUMMARY

Despite certain limitations in predictive power, the maximal exercise treadmill stress test, utilizing modern multistage protocols, has become a useful and dependable tool for the non-invasive diagnosis of the presence and severity of coronary artery disease. A test result must not be considered as a categorical disease/no disease classification, but should be seen as a quantitative risk factor, to be analyzed in concert with other patient screening data (e.g., history, physical examination, serum chemistry). In addition to electrocardiographic changes seen during the tests (especially the magnitude and duration of ST segment alteration), other symptomatic and hemodynamic responses are important in test interpretation. The level of stress at which a positive response occurs, the occurrence of a cardiac dysrhythmia, or an inappropriate blood pressure response may contribute to patient assessment.

The diagnostic accuracy of the treadmill test is described by Bayes' Theorem, which states that the predictive accuracy of a test is influenced not only by its sensitivity and specificity, but also by the prevalence of a particular disease in the population being studied. Given a currently accepted test sensitivity of 60-70%, and a specificity of 90%, the maximal treadmill test predictive accuracy can be seen to range from 16% (for a young asymptomatic population) to 86% (for a middle age population with classical angina).

Finally, the maximal exercise treadmill stress test has the following medical implications:

1) To help confirm a diagnosis of coronary artery disease in a patient with suspicious clinical signs or symptoms.
2) To assess the severity of disease and associated patient prognosis in a known case of coronary artery disease.
3) To prescribe exercise/work programs and evaluate modes of therapy in known disease, by measuring functional capacity.
4) To determine the presence and significance of cardiac dysrhythmias.
5) To screen apparently healthy asymptomatic populations, to help identify groups at higher than normal risk for coronary artery disease, but not to serve as a simple case finding device. Mass screening of populations expected to have substantial rather than insignificant prevalence of disease may prove more valuable, but even then only if the results are reviewed in conjunction with other screening techniques (e.g., coronary artery disease risk factor analysis).

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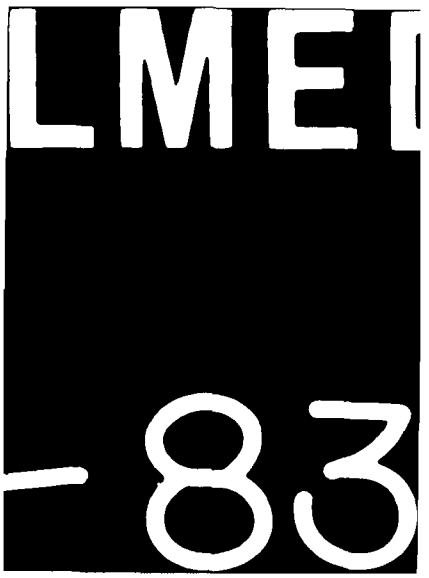
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